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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,497	02/24/2004	Mark W. Becker	249.P2	9922

25000 7590 06/06/2007

GILEAD SCIENCES INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

EXAMINER	
MARTIN, PAUL C	
ART UNIT	PAPER NUMBER
1657	
MAIL DATE	DELIVERY MODE
06/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/785,497	**Applicant(s)** BECKER ET AL.	
	Examiner Paul C. Martin	**Art Unit** 1657	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 14 May 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *19 April 2007*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,3-13 and 15-17*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Claims 1, 3-13 and 15-17 are pending in this application and were examined on their merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 07/19/04 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement was considered by the examiner.

Specification

The use of the trademarks CHIRALPAK© and ZORBAX© has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology (see above). Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The Applicant's disagreement with the citation of the Shaw et al. reference as necessitated by the amendments to the claims, and as being applicable to the original as well as the amended claims, and the request for finality of the rejection to be withdrawn is noted. However as this is a petionable issue and no petition has been received, Finality of the Action is maintained.
The MPEP states:
Any question as to prematureness of a final rejection should be raised, if at all, while the application is still pending before the primary examiner. This is purely a question of practice, wholly distinct from the tenability of the rejection. It may therefore not be advanced as a ground for appeal, or made the basis of complaint before the Board of Patent Appeals and Interferences. It is reviewable by petition under 37 CFR 1.181. See MPEP § 1002.02(c).

Claim Rejections - 35 USC § 102/103

Claims 1 and 3-7 remain rejected under 35.U.S.C § 102(b) as being anticipated by Shaw et al. (1997) for reasons of record set forth in the action mailed 12/19/06.

Claims 1, 3-7 and 10-13 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Shaw et al. (1997) for reasons of record set forth in the action mailed 12/19/06.
Claims 1, 3-7, 9-13, 15 and 16 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Shaw et al. (1997) in view of Glazier et al. (US 5,627,165) for reasons of record set forth in the action mailed 12/19/06.

Claims 1, 3-8, 10-13 and 17 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Shaw et al. (1997) in view of Starrett et al. (US 5,663,159) for reasons of record set forth in the action mailed 12/19/06.

Response to Arguments

Applicant's arguments filed 05/14/07 have been fully considered but they are not persuasive.

The Applicant argues that the Shaw et al. reference is a bioavailability assay to determine the stability of prodrugs against hydrolysis and does not have the objective of determining differential antiviral or antitumor activity in sampled tissues (Remarks, Pg. 7, Lines 7-13); and that plasma is not a tissue as defined by the Applicant's specification (Pg. 7, Lines 14-19).

This is not found to be persuasive for the following reasons, as discussed in the prior office action repeated below, Shaw et al. teaches every step of the claimed invention comprising the steps of; providing an amino acid phosphonoester prodrugs of PMPA (Pg. 1825, Table 1), selecting a target tissue (plasma) and non-target tissues (liver and intestine), administering the prodrug to both tissues and determining the relative in vitro biological stability and bioavailability of PMPA in the tissues (Pg. 1827, Column 1, Lines 7-8 and Column 2, Lines 1-14 and Table 3, and Pg. 1828, Column 1, Lines 1-10).

Shaw et al. teaches wherein the prodrug of PMEA was shown to significantly increase the oral bioavailability of PMEA in HIV infected patients and wherein PMPA has selective and potent inhibitory activity in vitro against retroviruses and wherein IV PMPA has been shown to reduce viral load in HIV infected patients (Pg. 1824, Column 2, Lines 1-9 and 16-18).

Shaw et al. teaches the administration of the PMPA prodrug to live dogs and the determination of the relative activity by analysis of the animal tissue after administration of the prodrug, wherein the activity is determined the amount of PMPA in the tissue (Pg. 1827, Fig. 2).

It is inherent in the method of Shaw et al. that the screening method would determine the relative antiviral activity conferred by the PMPA prodrug in the target and non-target tissues because PMPA is a known potent antiviral compound and the determination of the biological stability and bioavailability of prodrug derived PMPA in various tissues would necessarily also provide a determination of the relative

antiviral activity of the prodrug in those tissues even if no virus were present in the tissues.

Further, the Applicant's disputation of plasma as not being a tissue as defined by the Specification is puzzling as the Specification only requires that "tissue" shall be construed to be synonymous with cells of a particular source, origin or differentiation stage. Blood plasma and the cells therein certainly falls within this extremely broad, interpretation as would cells from any part of the body.

The Applicant's arguments that the administration of prodrugs to live dogs simply determines the ability of the prodrug to produce active drug in the circulation and does not disclose administering the prodrug and then assaying its conversion to parental drug in both target and non-target tissues (Remarks, Pg. 7, Lines 23-26), and that Applicant's method contemplates determining differential activity in various tissues (Remarks, Pg. 8, Lines 1-2) is not found to be persuasive for the following reasons:

As discussed in the prior action, Shaw et al. teaches the administration of the PMPA prodrug to live dogs and the determination of the relative activity by analysis of the animal tissue (plasma) after administration of the prodrug, wherein the activity is determined the amount of PMPA in the tissue (Pg. 1827, Fig. 2). It is inherent in the method of Shaw et al. that the screening method would determine the relative antiviral activity conferred by the PMPA prodrug in the target and non-target tissues because PMPA is a known potent antiviral compound and the determination of the biological stability and bioavailability of prodrug derived PMPA in various tissues would necessarily also provide a determination of the relative antiviral activity of the prodrug in those tissues even if no virus were present in the tissues. The obviousness and motivation for modifying the method of Shaw et al. to include performing the screening method in both target and non-target tissues of an animal were discussed in the prior action.

The Applicant argues that the Examiner allegedly acknowledges that Shaw et al. do not administer the prodrug to an animal and then determine the activity of the drug in individual tissues after administration (Remarks, Pg. 8, Lines 8-12).

This supposition is fundamentally flawed, as discussed above, Shaw et al. teaches the administration of prodrug to an animal and then determines the levels of bioavailable parental drug which inherently determines the relative antiviral activity conferred by the PMPA prodrug in the target and non-target tissues because PMPA is a known potent antiviral compound and the determination of the biological stability and bioavailability of prodrug derived PMPA in various tissues would necessarily also provide a determination of the relative antiviral activity of the prodrug in those tissues even if no virus were present in the tissues.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In this case, the adaptation of the method of Shaw et al. for screening a prodrug levels in plasma and tissue homogenates to screening for prodrug levels in intact animals would have been obvious to one of ordinary skill in the art because based upon scientific reasoning: Intact animals are more complex and variable systems than cell homogenates and the translation of in vitro methods to in vivo applications is well-known to those of ordinary skill in the art at the time of the instant invention.

The Applicant argues that it would not be obvious to combine the screening methods of Shaw et al. and Glazier et al. because Glazier et al. allegedly does not teach determining antiviral activity in different test tissues, but rather between infected and uninfected samples of the same tissues, while Shaw et al. are allegedly not looking for antiviral activity but rather at prodrug stability in individual tissues, and that a combination of the two would, in Applicant's view have Shaw et al. testing stability in infected and uninfected homogenates and finally, that there would be no reason to drop the intestinal homogenate since it is central to the method of Shaw et al. (Remarks, Pg. 9, Lines 1-16).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as discussed above Shaw et al. does teach inherently the relative antiviral activity of prodrugs in individual tissues and it is through combination with the Glazier et al. reference that the limitations not found in Shaw et al. are addressed. It is noted that Applicant readily admits on record that Shaw et al. do in fact, already know the antiviral activity of the parental drug (Remarks, Pg. 9, Lines 10-11) thus supporting the inherency argument put forth initially by the Examiner. Applicant's interpretation of the combined methods of Shaw et al. and Glazier et al. represents the Applicant's opinion and does not really address the obviousness and motivation to do combine the methods as set forth in the prior action.

The Applicant argues that Starrett et al. is duplicative or alternative to the bioavailability study of Shaw et al. and does not address the issue of antitumor activity (Remarks, Pg. 10, Lines 3-9).

The Applicant's arguments are not found to be persuasive for the following reasons; that Shaw et al. does in fact teach the claimed limitations of the instant invention (other than Claims 8 and 17) was discussed above. Obviousness to combine the references and motivation to do so was discussed in the prior action.

Conclusion

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul C. Martin whose telephone number is 571-272-3348. The examiner can normally be reached on M-F 8am-4:30pm.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul MartinExaminerArt Unit 1657

5/30/07

Continuation of 11. does NOT place the application in condition for allowance because: Claims 1, 3-13 and 15-17 are pending in this application and were examined on their merits.

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Conclusion

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JON WEBER
SUPERVISORY PATENT EXAMINER